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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/757,673	WILSON ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2005 and 04 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-10,12-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10, 12-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/10/04,9/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 7-10 and 12-35 are pending.

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be to directed to Brian Whiteman, Art Unit 1635.

Applicant's traversal and the addition of claims 27-35 in paper filed on 11/10/04 is acknowledged and considered.

The Declaration of James Wilson under 37 CFR 1.132 filed 11/10/04 is sufficient to overcome the rejection of claims 7-10, 18, and 23 based upon 102(e); and the rejection of claims 7-10, 18-24, 25-26 and claims 7-10, 12-17, 25-26 based upon 103(a) rejections because Dr. Wilson confirms Dr. Gao results.

The Declaration of Guangping Gao under 37 CFR 1.132 filed 11/10/04 is sufficient to overcome the rejection of claims 7-10 and 12-24 based upon 112 second paragraph, the rejection of claims 7-10, 18, and 23 based upon 102(e); and the rejection of claims 7-10, 18-24, 25-26 and claims 7-10, 12-17, 25-26 based upon 103(a) rejections because Dr. Gao shows that the subjecting the rAAV to four rounds of cesium chloride centrifugation the contamination is less than that taught by Podsakoff.

The provisional obviousness-type double patenting rejection of claims 7-10 and 12-26 is moot because of the cancellation of co-pending application 09/242,977.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence(s) of the specification or in an application data sheet by identifying the prior application by application number (37 CFR 1.78(a)(2) and (a)(5)). If the prior application is a non-provisional application, the specific reference must also include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

The status of US application 09/242,977 is missing. Applicants abandoned application'977.

Applicant's claim for domestic priority under 35 U.S.C. 120 to US application 08/708,188 filed on 9/6/96 (now US Patent 5,866,552) is acknowledged. However, the application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 25 and 26 of this application.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Claims 25 and 26: US application 08/708,188 does not recite the term "helper-free rAAV". US application '188 does not provide written support under 112 first paragraph for claims 25 and 26. Therefore, claims 25 and 26 only have priority to PCT/US97/15692 filed on 9/4/97.

Information Disclosure Statement

The examiner has considered the IDS filed on 9/30/04 and 11/10/04.

Claim Objections

Claim 27 is objected to because of the following informalities: The phrase "A method according to claim 7" is incorrect for the phrase in a dependent claim. Suggest amending the phrase to recite -- The method according to claim 7 --. Appropriate correction is required.

Claim 27 is also objected to because of the following informalities: The phrase "that contains less that" is grammatically incorrect. Suggest amending the phrase to recite – that contains less **than** --. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27 and 32-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation 'less that 1 infectious units of wild-type AAV per 10^9 rAAV' in new claim 27 is not supported by the as-filed specification. Applicant has cited pages 16 and 35 for support of new claim, however, there does not appear to be a written description of the claim limitation in the application as filed. See MPEP § 2163.06. Page 16, line 25 is directed a desirably dose of AAV and does there is no recitation of "less that 1 infectious units". Page 35, line 6 recites the phrase "at <1 infectious unit per 10^9 genomes of rAAV-F.IX.". However, the limitation in new claim embraces a genus of transgenes including Factor IX and is broader than AAV.FIX. Therefore, nothing in the specification would lead one to the particular limitation as set forth in the new claims.

> "It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose."
>
> *Lockwood v. American Airlines Inc.*, 41 USPQ2d 1961, 1966 (CAFC 1997).

Furthermore, new claims 32-35 are not supported by the as-filed specification. Applicant has cited pages 9, 29, and throughout the specification for support of the new claims, however, there does not appear to be a written description of the new claims in the application as filed. See MPEP § 2163.06. Page 9, lines 10-14 is directed to applicant's result of absence of inflammation upon administration of therapeutic doses of vector (C57BL/6 mice injected with lacZ AAV vector). Page 29, lines 10-15 is directed to intramuscular injection of lacZ AAV vector to C57Bl/6 and lacZ transgenic animals, which resulted in the animals not developing antibodies to beta-galactosidase. New claims 32-35 embrace a genus of administration routes, genus of muscle cells, and a genus of transgenes (including LacZ). The claims are broader than what is described in the instant specification. With respect to applicant's assertion that support for the new claims can be found throughout the specification, the examiner has made a thorough search of the specification and cannot find support for the new claims. Therefore, nothing in the specification would lead one to the particular limitation as set forth in the new claims. See *Lockwood v. American Airlines Inc.*, 41 USPQ2d 1961, 1966 (CAFC 1997).

Claims 7-10 and 12-24 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record set forth in the previous office action of 7-30-02 and 11-15-03.

Applicant's arguments filed 11/10/04 have been fully considered but they are not persuasive.

Applicant argues that the specification teaches that the rAAV is purified from sufficient amounts of contamination with helper adenoviruses that undesirable immune response are avoided and the specification teaches that this level of purity can be achieved by appropriate purification means known to one of skill in the art.

Applicant's argument is not found persuasive because the limitation "at least as free of adenoviral helper virus as is obtained by subjecting said recombinant AAV to four rounds of cesium chloride gradient centrifugation" is broader than performing four rounds of cesium chloride centrifugation as described in the instant specification. The limitation encompasses purification steps that are not supported by the specification and the phrase "at least" has no upper limit and causes the claims to read literally on embodiments outside four rounds of cesium chloride gradient centrifugation. For example, the limitation encompasses at least four rounds of centrifugation (e.g., five, six, seven, etc.). In addition, the limitation embraces fractionation methods, using size exclusion columns and other methods based on separation by size and density that are not disclosed in the instant specification. See In re Wertheim 541 F. 2d 257, 191 USPQ 90 (CCPA 1976).

The Declaration of either Guangping Gao or James Wilson under 37 CFR 1.132 filed 11/10/04 is insufficient to overcome the rejection of claims 7-10 and 12-24 based upon 112 first paragraph new matter rejection for the reasons of record and because neither Dr. Wilson nor Dr. Gao specifically address the new matter rejection.

Claims 32-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expressing a transgene in a skeletal muscle cell of a

mammal using intramuscularly administration of an rAAV, wherein the rAAV is purified of adenoviral helper such that an immune response is absent, does not reasonably provide enablement for a method of expressing a transgene in all muscle cells comprising introducing into the muscle cells a rAAV comprising a transgene wherein the rAAV is free of contamination with immunogenic adenoviral helper virus, wherein the rAAV is purified such that the transgene is expressed in the absence of destructive inflammation caused be contaminating helper adenovirus, wherein the rAAV is purified of adenoviral helper such that transgene is expressed in the absence of destructive immune response against contaminating adenoviral antigens, or wherein the transgene is purified of adenoviral helper such that transgene expression is a prolonged due to the absence of an antibody response against contaminating adenoviral antigens. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention encompasses a method of expressing a transgene in a muscle cell using a rAAV, wherein the rAAV is purified of adenoviral helper such that an immune response is absent. Instant claims 32-35 can read on a method of expressing a transgene in a muscle cell in vitro or in vivo. With regard to the claimed method practiced in vitro, applicants' disclosure does not teach the skilled artisan how to use this method in vitro. The only disclosed use for expressing a transgene in a muscle cell wherein the rAAV is purified of adenoviral helper such that an immune response is absent is for use in cells in vivo. These claims will therefore be evaluated based upon in vivo use.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an

artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

In an assessment of the gene therapy art at the time of the invention, Verma (CCT) noted " In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged." They further add, " But the problems- such as lack of efficient delivery systems, lack of sustained expression, and host immune response reactions-remain formidable challenges" (see the abstract). Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story" (see first and second paragraphs in col. 1 on page 239).

Anderson (BBX) notes that since the approval of first clinical trial of gene therapy protocol in 1990, more than 300 protocols have been approved worldwide. He further adds, "The conclusions from these trials are that gene therapy has the potential for treating a broad array of human diseases and that the procedure appears to carry a very low risk of adverse reactions; the efficiency of gene transfer and expression in human patients is, however, still disappointingly

low. Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease."

Regarding the issue of administration and absence of immune response, Monahan (BBY) noted, "A significant caveat to these conclusions is that the cellular immune response to rAAV appears to depend on the route of administration. Brockstedt et al32 have used rAAV encoding ovalbumin to look at CTL and antibody response in C57B1/6 mice following intraperitoneal, intravenous, subcutaneous, or intramuscular delivery. The intramuscular delivery was the only route that did not develop CTL responses, while all routes led to antibody production against the transgene and the vector." Therefore, an artisan would have expected to lack or absence of immune response only when the vector was administered by intramuscular route.

Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art.

Additionally, the specification only teaches the injection of the virus in the muscles (see pages 28-36, 38-41, and 43-45). The instant specification does not provide any guidance as to how an artisan of skill would have administered by any route other than intramuscular injection without producing immune response and as noted above even 4 years after the filing date of the invention (instant application claims priority to 9/6/96), the art did not teach as to how to administer AAV vector by any route other than intramuscular injection and in fact the cited art of Monahan et al teaches that other routes produce an immune response. Therefore, an artisan of skill would have to carry out extensive experimentation to find conditions that would have not produced immune response and such experimentation would have been undue since such was not routine in the art at the time of the invention.

The specification as filed is not enabling for the claimed invention commensurate with the scope of the claims because the specification does not provide sufficient guidance as to how an artisan of skill would have practiced the claimed invention and the artisan would have required extensive experimentation to make the viruses embraced by the scope of the claims and such experimentation would have been considered undue because the method of using such vectors was not routine in the art and the art of delivering a transgene in vivo was unpredictable. In conclusion, the art of gene therapy is highly unpredictable in general.

Accordingly, as discussed above, the specification as filed and the prior art do not provide sufficient guidance for an artisan of skill to have used the claimed invention without undue experimentation and therefore, limiting the scope of the claimed invention to a method of delivering a transgene to a skeletal muscle cell of a mammal, wherein said method comprises the step of administering to the skeletal muscle cell intramuscularly the composition comprising the rAAV and wherein the transgene in the composition is expressed in the mammal and wherein a cytotoxic immune response directed against rAAV-transduced cells of the mammal expressing transgene product is absent in the mammal, is proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Dwarki et al. (US 6,221,646) can be used in a prior art rejection against the instant claims 25 and 26 for the reasons set forth under priority.

Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiorini (AAB) taken with Dwarki et al. (US 6,221,646).

The instant specification defines "helper free rAAV" as substantially free of contamination with adenovirus or wild-type AAV or substance absence of helper virus or other exogenous helper molecules (page 7, lines 25-34). The definition of the term in the instant specification does not limit the rAAV to rAAV that have only been subjected to four rounds of CsCl gradient centrifugation or rAAV that is 100% free of helper virus, AAV, or other

exogenous molecules. Thus, the limitation can read on rAAV that is 60, 70, 80, 90, 95%, 99, or 99.9% helper free.

Chiorini teaches intramuscularly delivering a composition comprising AAV comprising a nucleotide sequence and a carrier (column 3). Chiorini teaches that the nucleotide sequence can encode Factor IX, insulin, and apoE (column 3). However, Chiorini does not specifically teach using helper free rAAV in the method. In addition, Chiorini does not specifically teach using a nucleotide sequence encoding growth hormone in the method.

However, at the time the invention was made, Dwarki teaches that a simple and efficient method is needed for producing rAAV. Dwarki teaches the production of rAAV substantially free of helper virus suitable for gene therapy and teaches a method for delivering to host cells a composition comprising a replication-defective recombinant AAV virions substantially free of wild-type AAV and helper adenovirus, wherein the virions comprise a nucleotide sequence (columns 1 and 14). Dwarki further teaches that the nucleotide sequence can encode Factor IX, insulin, and growth hormone (columns 4 and 9). However, Dwarki does not specifically teach intramuscularly delivering a composition comprising AAV and a carrier to a mammal.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Chiorini taken with Dwarki, namely to use rAAV substantially free of helper virus in a method of intramuscularly administering a composition comprising rAAV comprising a nucleotide sequence. One of ordinary skill in the art would have been motivated to use rAAV substantially free of helper virus taught by Dwarki in the method because Dwarki teaches that the helper free rAAV are suitable for gene therapy and can be produced using a simple and efficient method. In addition, one of ordinary skill in

the art would have been motivated to combine the references to intramuscularly administer said composition comprising rAAV and a carrier to a mammal because Chiorini teaches that intramuscularly a composition comprising AAV is a routine delivery route for one of ordinary skill of the art for delivering AAV to a mammal.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Chiorini taken with Dwarki, namely to deliver a nucleotide encoding Factor IX, apoE, beta interferon, insulin, or growth hormone to the mammal using the method. One of ordinary skill in the art would have been motivated, as a matter of design choice, to combine the references to use a nucleotide encoding a secretable protein in the method, wherein the protein is selected from Factor IX, apoE, beta interferon, insulin, and growth hormone because these proteins were well known to one of ordinary skill in the art for use in a method of delivering a transgene to a mammal using an rAAV.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 25-26 have been considered but are moot in view of the new ground(s) of rejection.

Claims 7-10, 18-23, and 25-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Podsakoff et al (AI) taken with Colosi (US 6,004,797).

Podsakoff et al. teach a rAAV for gene therapy wherein the gene encoding human erythropoietin is under the control of the CMV immediate early promoter, has SV40 polyadenylation sequences at the 3' end, and these sequences are flanked by 5' and 3' AAV ITRs

(columns 9-10, 16-17, and 21-22). Podsakoff et al. also teach that RSV promoter and other promoters can also be used for driving the expression of the gene of interest (columns 10-11). They also discuss the drawbacks of using adenoviral vectors for gene therapy, such as the elicitation of immune response to viral proteins, which would preclude subsequent treatments (column 1). Podsakoff et al. teach to purify the rAAV preparation by cesium chloride (CsCl) gradient centrifugation (column 14). Podsakoff et al. also teach to inject the rAAV vector in mice intramuscularly in heart and cardiac muscles (columns 19-20) and that erythropoietin is secreted by the myotubes or myoblasts (columns 4, 9-10 and 21-22). Podsakoff further teaches that human EPO gene was used as an example and that other suitable DNA sequences could be used that encode for proteins used for the treatment of different diseases (column 10). However, Podsakoff et al does not specifically teach an rAAV vector composition comprising 5' ITR, nucleic acid sequence encoding a secretable protein, and 3'ITR, wherein the level of contaminating helper virus (e.g., adenovirus) is no greater than that obtained by subjecting said recombinant rAAV to at least four rounds of cesium chloride centrifugation.

However, at the time the invention was made, Colosi teaches the problems associated with producing rAAV using helper virus or purifying the rAAV using a cesium chloride gradient (columns 2-3). Colosi teaches a method of producing rAAV comprising a heterologous nucleic, wherein the rAAV is free of helper virus (e.g. adenovirus) (column 5). Colosi further teaches that rAAV can comprise a transgene operably linked to a promoter (columns 2 and 10-11). Thus, one of ordinary skill in the art would reasonably determine that Colosi teaches a helper free rAAV or rAAV that is at least free of adenoviral helper virus as obtained by subjecting said

rAAV to at least four rounds of cesium chloride because Colosi does not require using adenovirus to produce rAAV.

At the time of the invention, it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teaching of Podsakoff and Colosi to produce a composition comprising rAAV and a carrier, wherein said rAAV comprises 5' AAV ITR, nucleic acid encoding human apoE operably linked to a promoter and a 3" AAV ITR, wherein the rAAV is at least free of helper virus by subjecting the rAAV to CsCl gradient centrifugation. One of ordinary skill in the art would have been motivated to use the method of producing rAAV that is free of helper virus taught by Colosi instead of the method of producing rAAV taught by Podsakoff because Colosi teaches overcoming the problems of producing rAAV with a helper virus or the problems of using a CsCl gradient to purify the rAAV and producing a titer of rAAV that is equivalent or greater than using a helper virus to produce the rAAV (column 9).

In addition, at the time of the invention, it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teaching of Podsakoff and Colosi to use a composition comprising rAAV and a carrier, wherein said rAAV comprises 5' AAV ITR, nucleic acid encoding human apoE operably linked to a promoter and a 3" AAV ITR, wherein the rAAV is at least free of helper virus by subjecting the rAAV to CsCl gradient centrifugation in a method of expressing a human apoE in a mammal by way of intramuscularly administering. One of ordinary skill in the art would have been motivated to use the rAAV in the method because the immune response in the mammal to the rAAV would be reduced because of the absence of adenovirus, which is a problem associated with gene therapy as exemplified by Podsakoff (column 1). In addition, regarding the limitations in instant claims 32-35, one of ordinary skill in

the art would have reasonably expected that using the rAAV taught by Colosi in the method taught by Podsakoff would result in an absence of an antibody response/inflammation response/cytotoxic immune response against contaminating adenoviral antigens because Colosi did not use adenovirus to produce the rAAV.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 7-10, 18-23, and 25-35 have been considered but are moot in view of the new ground(s) of rejection.

Claims 7-10, 12-17, and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Podsakoff taken with Colosi as applied to claims 7-10, 18-23, and 25-35 above, in further of view of Fang et al 1995 (CS) and Kay et al (US 5,980, 886).

However, Podsakoff et al. taken with Colosi do not specifically teach rAAV comprising transgenes encoding factor IX, beta-interferon, insulin, erythropoietin, growth hormone, and parathyroid hormone.

However, at the time the invention was made, Fang et al teach gene therapy of hemophilia B using adenovirus mediated factor IX expression (see the abstract). They also teach that adenovirus mediated gene transfer in vivo results in only transient gene expression due to the destruction of adenovirally transduced cells by the host immune system (see first para of the introduction section). Fang et al also teach an adenoviral vector that contains the cDNA encoding factor IX protein (materials and methods section on page 1040).

At the time of the invention, it would have been prima facie obvious to one of ordinary skill in the art to modify the rAAV vector of Podsakoff et al. taken with Colosi by cloning the factor IX cDNA in it and use the resultant vector in gene therapy of hemophilia by injecting with reasonable success because the methods of making rAAV vector and gene delivery in muscles are taught by Podsakoff while Fang et al. teach a factor IX vector from which the factor IX cDNA sequences can be spliced out. One of ordinary skill in the art would have been motivated to use an adeno-associated viral vector in place of adenoviral vector because Fang et al. teach that adenoviral vector mediated gene delivery results only in transient gene expression due to immune response and therefore, an one of ordinary skill in the art would have used an alternative method of gene therapy to increase the length of gene expression.

Regarding the other proteins recited in instant claims 9 and 26, it is noted that at the time the invention was made, the cDNAs encoding the recited proteins were known to one of ordinary skill in the art and were subject of preparing vectors for expression of these proteins. For example, Kay et al (US 5,980, 886) taught a vector for expression of proteins in liver and they listed insulin, growth hormone, erythropoietin, ApoE, parathyroid hormone, interferons, and several other proteins that could be expressed using their vector system (column 3). Therefore, one of ordinary skill in the art would have been enabled to make recombinant AAV expressing recited proteins, such as insulin, growth hormone, erythropoietin, ApoE, parathyroid hormone, interferons, at the time of the claimed invention with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make such vectors because all these proteins were known to be associated with a disease therefore, making such vectors would have helped in devising and developing therapeutic strategies.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 7-10, 12-17, and 24-26 have been considered but are moot in view of the new ground(s) of rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7-10 and 12-24 remain and claims 25-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,866,552 (Wilson JM et al., 2-2-1999) for reasons of record set forth in the previous office action of 11-23-01.

Applicants' request that this rejection be deferred until allowance is acknowledged.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764.

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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